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Acquired von Willebrand's Disease: A Concise Review

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Acquired von Willebrand's disease (AvWD), an adult-onset bleeding diathesis, has most commonly been found in patients with an underlying lymphoproliferative disease or monoclonal gammopathy. Other malignancies, autoimmune diseases, hypothyroidism, and drugs have also been associated with AvWD. We have included an illustrative case history of a patient with a bleeding diathesis consistent with AvWD and a monoclonal gammopathy who required emergent cardiac surgery. Our review of the literature determined that most cases of AvWD are due to a circulating antibody that combines with the high molecular weight multimers (HMWM) of von Willebrand factor (vWF). These vWF multimer-antibody complexes are subsequently cleared from the circulation either by the reticuloendothelial system or by adsorption onto tumor cells. Clearance of the HMWM of vWF thus results in extremely low functional levels and variable antigenic levels. Mixing studies which are traditionally used to diagnose factor inhibitors are useful only if removal of vWF-antibody complexes can be accomplished in vitro. Treatment with intravenous immunoglobulin has recently been shown to be the most effective therapy for patients with an underlying lymphoproliferative disorder or monoclonal gammopathy. This therapeutic strategy is based on the observed immune complex clearance phenomenon that appears to be operative in most cases. Other AvWD-associated diseases require treatment specifically directed at the underlying disorder. Am. J. Hematol. 54:139–145, 1997

Key words: von Willebrand's disease; acquired; inhibitor; therapy; pathophysiology

INTRODUCTION

Acquired von Willebrand's disease (AvWD) is an uncommon bleeding disorder that has remained, until recently, both difficult to characterize pathophysiologically, and challenging to treat successfully. Acquired forms of von Willebrand's disease are usually encountered in adults without a personal or family history of bleeding diatheses [1]. Laboratory examination demonstrates that the functional assay for von Willebrand factor (vWF), ristocetin cofactor activity (vWF:RiCo), is characteristically low or nearly absent, while the antigen (vWF:Ag) assay is low or normal [2]. Bleeding time is markedly prolonged. Furthermore, electrophoresis of von Willebrand factor most commonly reveals a pattern similar to type II congenital von Willebrand's disease (vWD), with selective loss of high molecular weight multimers (HMWM) [2,3]. In this paper, we discuss an illustrative case and review the recent literature on AvWD, which details the physiologic basic for this disease and the rationale for treatment options.

CASE HISTORY

A 55-year-old man presented with severe epistaxis requiring nasal packing and balloon tamponade. The patient complained of exertional chest pain for the past 2 weeks; he now noted dyspnea and chest pain at rest. He was found to have an hematocrit of 22% and an elevated PTT, and he was transfused to a hematocrit of 30% with relief of his resting pain. Stress thallium showed diffuse, reversible perfusion defects in the anterior, apical, inferior, and septal areas, while an echocardiogram showed normal systolic function. The patient was referred to the University of Maryland Medical Center for cardiac catheterization and evaluation of his bleeding disorder.

The patient's past medical history and family history

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TABLE I. Laboratory Values of Patient Upon Admission to Our Hospital

Creatinine	0.9 mg/dl
Hematocrit	32.8%
Platelets	75×10^9/l
PT (INR)	1.1
PTT	39 sec (22–33)
Reticulocytes	5.1%
Lupus anticoagulant	Negative
Factor IX	102%
Factor XI	82%
Factor VIII	14%
Thrombin time	14.8 sec (nl)
Fibrin split products	<10 mcg/ml
vWF:Ag	13%
vWF:RiCo	0%

TABLE II. Disorders Associated With Acquired von Willebrand's Disease and Their Approximate Frequencies in the Referenced Cases

Monoclonal gammopathy of unknown significance	27%
Multiple myeloma	15%
Non-Hodgkin's Lymphoma	10%
Myeloproliferative disorders	10%
Wilm's tumor	8%
Drugs	7%
Chronic lymphocytic leukemia	5%
Hypothyroidism	5%
Carcinoma	3%
Hairy-cell leukemia	2%
Unknown	8%

were negative for any bleeding diatheses and were otherwise noncontributory. Physical examination was significant only for nasal packing without active bleeding. Pertinent admission laboratory values are shown in Table I. Serum studies demonstrated a monoclonal IgG kappa. A bone-marrow biopsy was normal. Angina continued, and cardiac catheterization demonstrated three-vessel coronary disease. Prior to coronary artery bypass grafting (CABG), he received a single dose of intravenous immunoglobulin (IVIG), 1 g/kg. All vWF assays returned to normal 1 day later, and he immediately underwent CABG without complication.

ASSOCIATED UNDERLYING DISORDERS

The first descriptions of AvWD were in the early 1970s, after assays to distinguish between factor VIII and vWF (previously termed factor VIII-associated antigen) became readily available. Case reports described adult-onset (or late childhood-onset) bleeding diatheses, with both prolonged bleeding times and partial thromboplastin times with a variety of underlying diseases [4]. Most cases have reported an associated monoclonal gammopathy with or without a lymphoproliferative disorder such as multiple myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia (Table II) [5–19].

Development of AvWD was usually simultaneous with the discovery of paraprotein in these patients; however, there are cases in which an underlying lymphoproliferative disease was found without gammopathy [7,9,13,18]. Therefore, lymphoproliferative disorders and/or monoclonal gammopathy are present in over 50% of reported cases of AvWD. IgG paraproteins are the most prevalent, occurring in 80% of cases with a monoclonal immunoglobulin; half of these are classified as monoclonal gammopathies of unknown significance (MGUS) [20–31]. Monoclonal IgM predominates as expected in patients with Waldenstrom's macroglobulinemia, and IgA, though less common, has occurred in several patients with underlying lymphoproliferative disorders [32] and in one patient without an underlying malignancy [26].

The next most commonly reported group of disorders associated with AvWD is the myeloproliferative disorders (MPD), especially essential thrombocythemia (ET) and polycythemia vera (PV) [33–37]. In the study by Budde et al. [33], 2 patients developed AvWD which fluctuated in severity with the cell counts, especially platelets. The level of vWF was lower when cell counts were elevated, and subsequently approached normal after treatment. Clinical bleeding appeared to correlate with changes in vWF levels. The overall incidence of AvWD in the setting of MPD is unknown. Budde et al. [33] identified 5 additional patients with MPD who had a vWF electrophoresis pattern similar to the 2 subjects with AvWD; however, these 5 patients were asymptomatic and had normal vWF:RiCo results. While it is unclear how many patients were screened to find these 5, only 10 such patients have been reported in the literature; thus, the association of AvWD with MPD is relatively uncommon.

AvWD has been infrequently reported in association with autoimmune diseases such as hypothyroidism, systemic lupus erythematosus (SLE), and scleroderma [16,38–42]. Hypothyroidism-associated AvWD has been reported in adults and adolescents, and appears to resolve with thyroid hormone replacement therapy [39,43].

The association of drugs and AvWD has been rarely reported. Ciprofloxacin, griseofulvin, valproic acid, and hydroxyethyl starch (HES) have been implicated as causes of AvWD [44–48]. In the single patient with HES-induced AvWD, the patient had an underlying astrocytoma and factor XII deficiency; AvWD was found after bleeding occurred 3 days after starting HES. Laboratory values returned to normal and bleeding ceased after discontinuation of the drug [46]. Ciprofloxacin-induced AvWD in 2 patients produced a vWF electrophoresis pattern identical to paraprotein-associated type II AvWD, although a workup for inhibitors and paraproteins was

negative [44,45]. The association with AvWD was strongly supported by resolution of bleeding and restoration of a normal vWF electrophoresis pattern after ciprofloxacin discontinuation. Griseofulvin-associated AvWD also resolved after discontinuation of the drug; however, this particular patient had a concomitant IgE gammopathy which simultaneously resolved. Thus, it is just as likely that AvWD in this case was caused by the paraprotein [46]. Finally, a series of 30 adolescents undergoing valproate therapy was studied for vWF abnormalities [47]. Patients tended to have a lower level of all vWF multimers than controls, but the median ristocetin cofactor activity was 63%, with the lower limit of normal being 70% activity. There was no comment regarding resolution following drug discontinuation. Although 19 of the 30 children reported bleeding during therapy, it is unclear if these symptomatic patients had abnormal laboratory values. Therefore, the association of AvWD and valproate is not clear and needs further study.

AvWD in one patient with excessive fibrinolysis of unclear etiology has been reported [49]. This patient had an underlying IgM gammopathy, and fibrinolysis was assumed based only upon a low fibrinogen concentration. There was no direct evidence that fibrinolysis was associated with AvWD, although there is a separate report that pharmacologically induced fibrinolysis may cause a decrease in ristocetin cofactor activity [50]. However, vWF:RiCo was much lower in the reported IgM case than in the transient decreases observed in patients by Federici et al. [50]. It is likely that the IgM gammopathy may have been the most significant factor associated with AvWD in this particular case.

Wilm's tumor, adrenal cell carcinoma, and other adenocarcinomas have been reported in association with AvWD [16,51–53]. Coppes et al. [51] screened 50 patients with Wilm's tumor and found 4 (8%) with AvWD. Although the presence of a monoclonal gammopathy in most of these patients was not investigated, all cases associated with Wilm's tumor or adrenal carcinoma had resolution of AvWD after successful removal of the tumor.

There has been one report of AvWD in a patient after bone-marrow transplantation [54]. That patient had reduction of all vWF multimers and was receiving therapy for graft-vs.-host disease (GVHD), tuberculosis, and bacteremic sepsis [54]. Therefore, it is unclear whether AvWD was associated with the drugs, GVHD, or infection with disseminated intravascular coagulation.

With respect to underlying disorders, AvWD is most commonly associated with lymphoproliferative diseases and monoclonal gammopathy, and less often with specific malignancies including MPD, Wilm's tumor, and adrenal adenocarcinoma. Monoclonal gammopathy appears to be the dominant factor in studies examining the pathophysiology of AvWD.

PATHOPHYSIOLOGY

High molecular weight multimers (HMWM) are the most hemostatically active multimers of vWF (Fig. 1A) by virtue of having larger numbers of several critical binding domains. One domain is the ligand for high-shear adhesion to platelet glycoprotein Ib (gpIb) [3]. A second binding site is the arg-gly-asp (RGD) sequence of vWF monomers, which mediate adhesion of HMWM to the platelet integrin, GPIIb/IIIa, and perhaps to integrins of other cell types [55,56]; a third domain binds to several types of collagen [10]. Ristocetin causes vWF to bind to platelet gpIb, causing agglutination of platelets. This reaction characteristically agglutinates platelets via HMWM in the absence of platelet activation, and is measured using light transmittance in a platelet aggregometer [57]. Most importantly, normal quantities of lower molecular weight vWF multimers will not provide effective platelet agglutination or hemostasis in the absence of HMWM; type II congenital vWD and AvWD are examples of selective loss of HMWM that results in a clinical bleeding diathesis [3].

Acquired bleeding disorders in general are often associated with development of an inhibitor, typically an antibody to the functional domain of a coagulation factor, such as an acquired factor VIII inhibitor. Laboratory workup demonstrates prolonged functional assays dependent on that factor (i.e., a prolonged PTT with a factor VIII inhibitor) which do not correct after mixing patient plasma with normal plasma. An inhibitor is operative in most cases of AvWD; however, the antibody in AvWD is usually directed to a nonfunctional domain on the vWF multimer (Fig. 1B) [10]. It is believed that after the antibody binds to vWF, the vWF-antibody complex is rapidly cleared from the circulation by the reticuloendothelial system (Fig. 1B), resulting in a vWF electrophoresis pattern demonstrating selective loss of HMWM (Fig. 1C) [10]. In contrast to classic inhibitors, ristocetin cofactor activity in AvWD will increase to near normal levels after mixing with normal plasma [5,6,10,12,14,15,17,18, 20,23–25,27,29–31,44]. This phenomenon occurs because the antibody-antigen complex is not cleared in vitro, and the active site for vWF is not blocked by the antibody. Only 5 of more than 65 reported cases of patients with AvWD [16,26,35] have documented a failure to increase vWF:RiCo after a 1:1 mixture with normal plasma [5,6,9,10,14,17,19–21,23,29–31,58].

Several investigators have shrewdly added staphylococcal protein A to in vitro mixing studies in order to remove antigen-antibody complexes and simulate the in vivo function of the reticuloendothelial system [9,16, 21,24,27,31]. As expected, addition of staphylococcal protein A to a 1:1 mix of patient and normal plasma resulted in a decrease in vWF:RiCo after initial normalization with mixing [9,16,21,24,27,31]. Other attempts

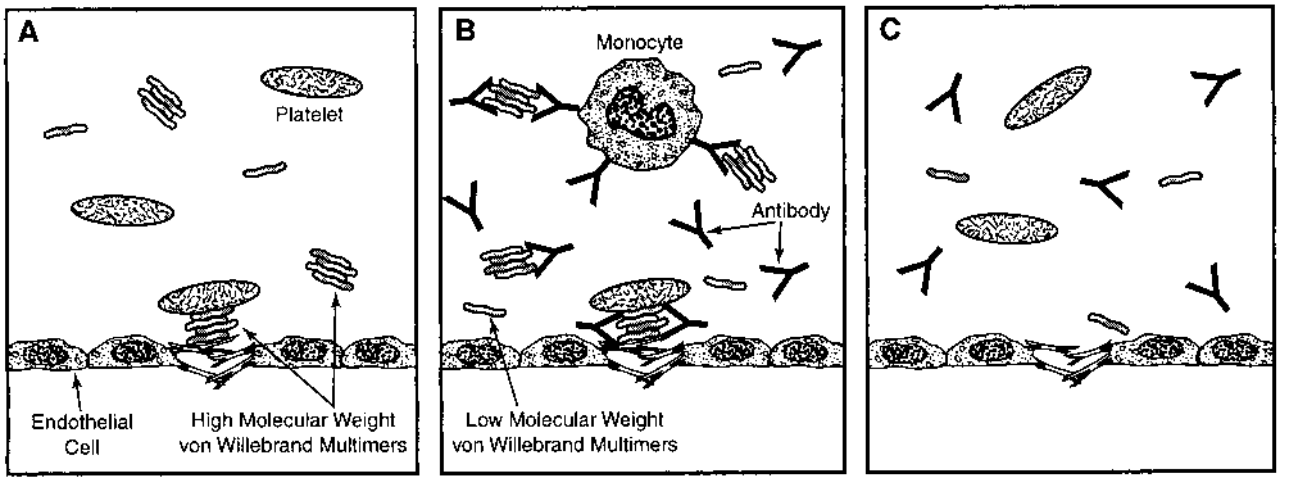

Fig. 1. Paraprotein-induced clearance of vWF in AvWD. A: Normal vWF hemostasis with high molecular weight multimers (HMWM) mediating binding of platelets to damaged subendothelium. B: When antibody binds to vWF in the setting of monoclonal gammopathy of unknown significance (MGUS) or lymphoproliferative disorders, the vWF-antibody complex is then cleared by the reticuloendothelial system. C: This results in preferential loss of HMWM and low ristocetin cofactor activity.

to simulate in vivo clearance have been successful by pelleting antibody-antigen complexes in a centrifuge before performing vWF:RiCo, or by using Fc-binding beads to elute off the complexes [6,34]. Recently, van Genderen et al. [8,10] showed that the normal collagen-binding activity of vWF was impaired in 2 patients with AvWD, even after the vWF:RiCo and vWF antigen levels had been normalized by mixing studies, suggesting that the collagen-binding domain is an antigenic site in some cases of AvWD.

Several investigators purified an immunoglobulin fraction from AvWD patients and added the immunoglobulin at concentrations of 2–5 g/l to normal platelets [4,12,16,17,24–27]; decreased aggregation in response to ristocetin was then demonstrated, indicating that the inhibitor was contained in the immunoglobulin fraction. Since there are rare cases when the ristocetin assay remains low when normal plasma is mixed with either patient plasma or patient immunoglobulin, the antibody may occasionally interfere with active sites in the vWF:RiCo assay when high immunoglobulin titers are present. Two other mechanisms are possible. Autoantibodies in AvWD may bind to active sites on the molecule, but only a few cases have a titer sufficient to decrease vWF:RiCo activity in mixing studies. Another possibility is that rare cases exist where antibody is directed against active sites on vWF but still causes rapid clearance in vivo (and a type II vWF electrophoresis pattern) and a decreased vWF:RiCo, even when mixed with normal plasma. However, most studies have shown that the classic diagnosis of a factor inhibitor is inoperative with AvWD, since the inhibitor is very infrequently detected in traditional mixing studies. In order to demonstrate clearly the presence of an inhibitor, in vitro simulation of in vivo clearance is almost always necessary. One question that currently remains unanswered is why the HMWM of vWF are preferentially cleared by the autoantibody in AvWD.

Occasionally, the pathophysiology of AvWD differs from that outlined above. Adsorption of vWF to tumor cells has been suggested as another mechanism of HMWM clearance [14,29,52]. These three studies demonstrated immunofluorescent staining of vWF inside tumor cells, and in the report by Facon et al. [52], AvWD resolved after removal of adrenal cell carcinoma. Interestingly, two reports involved patients with underlying myeloma and monoclonal gammopathy [14,29]. Both reports found similar results on mixing studies; however, experiments to elute the antibody-antigen complexes were not performed. In several cases of Wilm's tumor-associated AvWD, immunofluorescence for vWF was not detected on tumor cells; however, removal of the tumor was curative of the AvWD. Adsorption of vWF onto tumor cells is hypothesized to occur by vWF combining with either gpIb-like receptors or integrin ligands on tumor cells, or by vWF adhesion to a circulating antibody that then binds to Fc receptors on tumor cells. Scrobohaci et al. [29] provided direct evidence for the former by demonstrating that plasma cells in a patient with myeloma reacted with antibodies directed at several epitopes of gpIb. Tumor-cell adsorption of HMWM may also explain the association of myeloproliferative disorders and AvWD, in which lowering the cell counts results in resolution of AvWD; this may be especially true in AvWD associated with essential thrombocythemia [34]. Inhibitor studies and tumor-cell immunofluorescence for vWF have not been performed in most MPD patients; however, all of these patients had type II multimer patterns when investigated [33–37].

Lazarchick et al. [35] demonstrated normalization of vWF:RiCo after mixing with normal plasma in one patient with MPD. Interestingly, although antibody-antigen elution was not performed, the patient's purified polyclonal IgG did decrease the vWF:RiCo activity of normal plasma. This finding indicates that immunoglobulins may play a role in some cases of MPD-associated AvWD.

The pathophysiology of AvWD associated with drug therapy or fibrinolysis is unclear. Inhibitor studies were not performed in these patients, and monoclonal gammopathies were often present [44–47,49]. More rigorous investigation of AvWD in these situations is required.

THERAPY

Treatment of AvWD clearly depends on the underlying disease process and the mechanisms responsible for development of the syndrome. In early reports of AvWD, patients were treated as for congenital AvWD with high doses of cryoprecipitate; bleeding was usually controlled in the short term, and hemostasis corresponded with normalization of vWF:RiCo [6,8–10,12,15,24,27,28]. Similar to treatment for congenital vWD, factor replacement was costly and exposed the patient to the risk of transfusion-transmitted diseases. DDAVP has been used in some AvWD cases to transiently increase vWF levels and vWF:RiCo, but vWF:RiCo activity decreased within 2–3 hr, similar to treatment with cryoprecipitate [5,8,17, 18,20,21,27].

These short-lived results further supported previous hypotheses regarding antibody-vWF clearance, and led investigators to strategies aimed at the underlying pathology. Extracorporeal immunoadsorption was attempted in one patient with short-term success [7]; in this case, factor VIII concentrate containing significant amounts of vWF (Humate P) was infused soon after immunoadsorption, and vWF assays normalized. However, this therapy was very labor-intensive and expensive, and it required repeated treatments.

A possible use for intravenous immunoglobulin (IVIG) in AvWD was demonstrated by in vitro experiments by Handin et al. [4]. In that case report, the patient's vWF:RiCo was very low but returned to normal when the plasma was incubated with an anti-Fc IgG antibody prior to adding ristocetin. Since that study, there have been many reports of successful IVIG infusions for AvWD [13,19,20–23,27,30,34,42]. In general, 0.5–2 g/kg IVIG over 1–2 days produces an immediate and relatively lasting effect. Epistaxis, gastrointestinal hemorrhage, and other active bleeding problems usually resolve rapidly after IVIG infusion [19,21–23,27,30,34]. In most patients, as in our illustrative case, surgery may be performed as early as 1–2 days after IVIG infusion [13,20,42]. One caveat is that all of the cases with successful treatment by IVIG were associated with either a lymphoproliferative disorder or a monoclonal gammopathy. None of the patients with MPD, carcinoma, or drug-induced AvWD have been treated with IVIG, although the association of a paraprotein with some of these reported cases would make treatment with IVIG a reasonable option, especially in the acute setting. However, therapy of the underlying disorder in most instances may be more likely to resolve the long-term bleeding diathesis (see below).

The duration of vWF:RiCo normalization after IVIG is highly variable; most reports suggest an effect lasting 10–20 days [19,20,22,23,27,30,42]. Castaman et al. [21] found a short-lived effect of only 5 days after the initial dose of IVIG in one patient; however, later infusions achieved longer-lasting results (up to 20 days). In addition, repeat IVIG dosing reproducibly normalizes vWF:RiCo; in some patients, IVIG has been infused every 30 days to maintain a normal vWF:RiCO and successfully prevent recurrent bleeding [19,21,42]

When AvWD is presumed to be caused by a monoclonal immunoglobulin associated with a lymphoproliferative disorder, treatment of the underlying malignancy may provide long-term suppression of the paraprotein and presumably amelioration of the AvWD. Similarly, for AvWD associated with MGUS, a trial of intermittent high-dose dexamethasone (the most active single agent for plasma-cell disorders) should be considered to reduce the level of pathogenic immunoglobulin [59]. Depending upon the severity of either the underlying lymphoproliferative disorder or the AvWD, more intensive chemotherapy may be necessary; in cases of monoclonal IgM causing significant disease, a limited trial of 2-chlorodeoxyadenosine has been successful in other settings and could be considered for AvWD associated with IgM paraproteins [60].

AvWD patients without a monoclonal immunoglobulin or lymphoproliferative disorder require treatment targeted at their underlying disease. Treatment of myeloproliferative disorders with chemotherapeutic agents appears to be the most effective therapy when such patients develop AvWD [33,34,36,37]. This chemotherapy strategy is based on the hypothesis (so far unproven) that the proliferating hematologic clone binds and clears vWF rather than immune clearance by the reticuloendothelial system.

Discontinuation of drugs thought to cause AvWD appears to result uniformly in resolution of the disorder, and persistent disease has not been reported in patients with drug-induced AvWD [44–47]. Whether this represents clearance of vWF by a drug-hapten mechanism is unknown.

CONCLUSIONS

AvWD presents similarly to congenital vWD, with mucosal bleeding, an elevated PTT, decreased vWF:RiCo, and a type II vWF electrophoresis pattern in most cases.

A diligent search for lymphoproliferative disease and/or monoclonal gammopathy is warranted, since 57% of AvWD patients will have at least one of these two entities. In the remaining cases, AvWD has been associated with other malignancies, drugs, and, rarely, autoimmune disease. The diagnosis of AvWD is suggested by the lack of a prior clinical bleeding history and the extremely low vWF:RiCo. Mixing studies usually demonstrate an increase in vWF:RiCo after addition of normal plasma; in vitro removal of immune complexes in mixing studies appears to simulate the in vivo situation, resulting in a decrease in vWF:RiCo activity. The pathophysiology of most cases of AvWD involves antibodies directed at HMWM of vWF; HMWM-antibody complexes are presumably cleared by the reticuloendothelial system. Another possible mechanism of clearance is selective HMWM adsorption onto tumor cells via HMWM-antibody binding to Fc receptors, or direct HMWM binding to gpIb-like receptors or RGD-containing ligands on tumor cells. If a monoclonal immunoglobulin or lymphoproliferative disorder is present, intravenous immunoglobulin (IVIG) is the treatment of choice and usually results in a rapid and sustained response. Emergent elevation of plasma vWF levels and vWF:RiCo normalization can be achieved with cryoprecipitate, Humate P, or DDAVP, but is useful only for a few hours. If an underlying tumor or myeloproliferative disorder is found, treatment of that disorder may be curative in most cases of AvWD.

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